Review Article

Influenza H1N1 infection in immunocompromised host: A concise review

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ABSTRACT

Infleunza A (H1N1) infection has a propensity to infect an immunocompromised host (ICH). These patients experience more severe manifestations and related complications with increased mortality. Influenza A (H1N1) infection in ICH differs from non-ICH in terms of clinical features, range of complications, radiological features, treatment response, and outcome. Radiology may show higher number of lesions but with no or minimal corresponding clinical manifestations. Coinfection with streptococci, staphylococci, and *Aspergillus* further increases mortality. Antiviral resistance compounds the overall picture despite optimal regimen. Use of steroids is detrimental. Extracorporeal membrane oxygenation (ECMO) is usually avoided in ICH. However, ICH groups with influenza A (H1N1) infection complicated by acute respiratory distress syndrome who have received ECMO have recorded mortality up to 61%. Nevertheless, evidence-based recommendation on use of ECMO in ICH is lacking. Annual inactivated influenza vaccine is recommended for most ICH groups with a few exceptions and for their close contacts. Hygiene measures greatly contribute to reducing disease burden. High index of suspicion for influenza A (H1N1) infection in ICH, early antiviral therapy, and treatment of coinfection is recommended. With the threat of transmission of resistant viral strains from ICH to the community, apart from treatment, preventive measures such as vaccination and hygienic practices have a significant role. Through this review, we have attempted to identify clinical and radiological peculiarities in ICH with influenza A (H1N1) infection, treatment guidelines, and prognostic factors. Influenza A (H1N1) infection in ICH may remain clinically silent or mild.

KEY WORDS: Extracorporeal membrane oxygenation in immunocompromised, influenza-associated aspergillosis, influenza vaccine in immunocompromised, methicillin-resistant *Staphylococcus aureus* in H1N1

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INTRODUCTION

In March 2009, an outbreak of the pandemic influenza A (A/H1N1pdm09) viral infection was detected in Mexico. Soon after, the World Health Organization (WHO) declared a pandemic on June 11, 2009. It indicated widespread community transmission on at least two continents.[1] India reported its first pH1N1 influenza-positive case from Pune city on June 22, 2009, in a traveler from the USA. The first death in India due to pH1N1 influenza was on August 3, 2009.

Treating influenza A (H1N1) in immunocompromised host (ICH) poses peculiar challenges which will be discussed in this review. Here, ICH implies human immunodeficiency virus (HIV)-infected patients, patients with active malignancies, particularly hematological malignancies, chemotherapy and/or radiotherapy recipients, hematopoietic stem cell transplant (HSCT) recipients, solid organ transplant (SOT) recipients, patients on high-dose corticosteroid therapy (>2 weeks),[2] pregnant women, and pediatric population.

Access this article online	
Quick Response Code:	**Website:** www.lungindia.com
	DOI: 10.4103/lungindia.lungindia_464_18

VIROLOGY OF INFLUENZA VIRUS

Influenza viruses are RNA viruses of the Orthomyxoviridae family classified as influenza A, B, and C. Influenza A viruses are further subdivided as per the antigenic characteristics of their surface hemagglutinin (H) and neuraminidase (N) glycoproteins. Influenza A has 15 H and 9 N subtypes, of which only H1, H2, H3, N1, and N2 have caused extensive outbreaks in humans.[3]

The pandemic H1N1 influenza A virus (influenza A [H1N1] pdm09 virus) strain is a product of genetic reassortment, called asantigenic shift, resulting in a novel strain with new antigens. It represents a quadruple reassortment of two swine strains, one human strain, and one avian strain of influenza.[4]

EPIDEMIOLOGY OF INFLUENZA A (H1N1) IN IMMUNOCOMPROMISED HOST

As compared to seasonal influenza, peak occurrence of H1N1 pneumonia is not related to extremes of age. Patients >65 years of age possibly possess preexisting immunity against antigenically similar influenza viruses that circulated prior to 1957.[5] Hemagglutinin inhibition (HI) titers >1:40 is considered to represent good antibody response.[6] One study showed lower levels of cross-reactive antibodies to the influenza A (H1N1) pdm09 virus among individuals <70 years age compared to those ≥90 years age (6% vs. 88%, respectively, had HI titers >1:40).[7]

We focused on literature from 2009 onward with most of it dedicated to pH1N1 influenza. For epidemiology, we reviewed nine indexed publications[2,8-15] [Figure 1] on influenza A (H1N1) in ICH subgroups except pregnancy. Overall, male preponderance and higher frequency in adults was noted. In addition, other studies suggested that pregnant women, especially in the third trimester[16,17] and obese patients[18] were more prone to influenza A (H1N1). Data on vaccination status was insufficient. Four continents (North America, South America, Europe, and Oceania) were represented in the studies above. Unfortunately, no robust data representing the developing countries were available.

CLINICAL FEATURES OF INFLUENZA A (H1N1) IN IMMUNOCOMPROMISED HOST

Memoli *et al.* have found fewer overall influenza symptoms in ICH. They postulate that although the cytokine response to acute infection in ICH is similar to non-ICH, ICH shows a blunted illness with minimal or no clinical manifestations.[8]

PECULIAR ISSUES OF INFLUENZA A (H1N1) IN IMMUNOCOMPROMISED HOST

ICH, particularly with pH1N1 influenza are more prone to severe influenza-associated complications, prolonged viral shedding, bacterial or fungal coinfections, and emergence
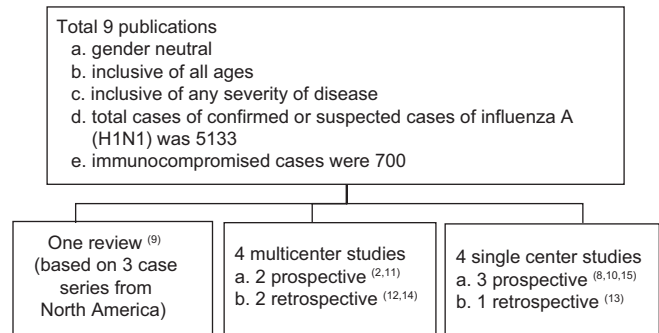

Figure 1: Studies included in the review for epidemiology

of antiviral drug resistance.[19] ICH tend to have more severe disease with higher morbidity and mortality.[20-22]

The most common complication is pneumonia. Neurologic complications in decreasing order of frequency include seizures including status epilepticus, encephalopathy or encephalitis, meningitis, and Guillain–Barre syndrome.[23] Systemic complications include bronchiolitis, status asthmaticus, myocarditis, pericarditis, rhabdomyolysis, renal insufficiency, toxic shock syndrome, and multiorgan failure.[24]

Prolonged viral shedding in ICH with influenza A (H1N1) despite antiviral therapy results in longer hospitalization albeit with a shorter ICU stay, in ICH and an eventual poorer outcome.[8]

Immunocompromised patients are more prone to co-infections by bacterial and fungal pathogens. Increased susceptibility to coinfection in ICH with influenza A (H1N1) by bacteria or fungi can be explained thus. Pulmonary epithelial cell injury caused by the replicating influenza virus exposes potential attachment sites for bacterial or fungal invasion and impairs the clearance of secretion from the respiratory tract. Alternatively, phagocytosis by alveolar macrophages and chemotaxis of polymorphonuclear leukocytes may be inhibited after influenza infection.[25]

In cases of pH1N1 influenza with bacterial coinfection, the pathogens in respiratory secretions identified in decreasing order of frequency are *Staphylococcus aureus*, *Pseudomonas* species, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes,* and other bacteria. Among *S. aureus,* methicillin-resistant *S. aureus* (MRSA) constitute 48%.[26] Smaller studies with conflicting results will not be discussed. Typical picture of MRSA coinfection after pH1N1 influenza is of a previously healthy young adult presenting with severe pneumonia with hemoptysis, hypotension followed by rapid progression to septic shock, and respiratory failure requiring ventilatory support. MRSA-induced necrotizing pneumonia is associated with high fatality rate.[26,27]

Vanderbeke *et al.*[28] in their compact review on influenza-associated aspergillosis (IAA) found that

majority of their patients were immunocompromised. Morbidity and mortality was high with 57% deaths. Garnacho-Montero et al.[2] reported 100% mortality in cases of ICH with influenza A (H1N1) and IAA. Underlying pathogenesis is similar to bacterial coinfection.[28] Clinical presentation of IAA is worsening of respiratory symptoms after initial improvement. Complications such as acute respiratory distress syndrome (ARDS), secondary bacterial infections, oseltamivir-resistance, or pulmonary hemorrhage can lead to stormy clinical course in ICH.[29]

DIAGNOSIS OF INFLUENZA A (H1N1)

Real-time reverse transcriptase polymerase chain reaction (rRT-PCR), especially with combined nasopharyngeal and throat swabs with nasopharyngeal aspirates is the most sensitive and specific test for the diagnosis of influenza A (H1N1). Viral culture has similar sensitivity but is too slow to help guide clinical management. A negative viral culture does not exclude influenza A (H1N1). Rapid antigen test and immunofluorescent antibody (direct or indirect) tests can distinguish between influenza A and B viruses. However, they cannot subtype the pandemic and seasonal strains. This can only be done by rRT-PCR or culture.[30,31] Serologic testing for HI titer is most useful for influenza surveillance.[32]

DIAGNOSTIC CHALLENGES OF INFLUENZA A (H1N1) IN IMMUNOCOMPROMISED HOST

Rapid diagnosis of influenza in ICH is vital because delay in antiviral initiation is associated with poorer outcome.[12,16,17,33] A few studies have underscored the effect of influenza on morbidity and mortality in ICH. In HSCT recipients, influenza causes higher incidence of pneumonia[34] and mortality up to 43%.[35] In renal transplant recipients with pH1N1 influenza, there is increased allograft dysfunction. In SOT recipients, there is higher incidence of myocarditis[36] and pneumonitis[37] and mortality up to 7%.[12] In HIV-infected cases, higher incidence of pneumonia and mortality occurs.[38] In hematological malignancies and chemotherapy (for solid tumors) recipients, we see increased pneumonia.[39]

Garcia-Vidal C et al.[29] concluded that reverse transcriptase PCR is superior to direct fluorescence assay for detection of influenza virus in ICH. Furthermore, direct fluorescence assay shows low yield in viral detection in samples collected in the early days of symptom onset. Lower respiratory tract sample has a higher diagnostic yield. Notwithstanding, positivity in a lower respiratory tract sample portends worse outcome.[40]

RADIOLOGY IN IMMUNOCOMPROMISED HOST

Higher number of radiographic abnormalities is noted in ICH, suggestive of increased risk of pulmonary involvement and complications. Ironically, clinical manifestations are minimal.[8] Extensive pulmonary infiltrates (median Murray score 3) have been reported.[15] In 14 critically ill patients with probable or confirmed pH1N1 influenza, extensive disease involving ≥3 lung zones was observed in 13. Nodular opacities and pulmonary emboli were reported on computed tomography (CT) chest imaging.[41] However, prognostic implications of radiological abnormalities are not well studied.

DIAGNOSIS OF INVASIVE PULMONARY ASPERGILLOSIS IN IMMUNOCOMPROMISED HOST

Diagnosis of invasive pulmonary aspergillosis (IPA) in ICH is difficult. While histological identification of acute-angle branching septated hyphae is ideal to prove IPA, lung biopsy in critically ill or ICH is not feasible. Characteristic CT finding of "halo-sign" of IPA might be absent in IPA.[28] Bronchoscopy provides the solution. It allows collection of bronchoalveolar lavage fluid (BAL) and visualization of the trachea and bronchi. Galactomannan antigen detection and culture on BAL has good sensitivity in IAA, (94% and 78%, respectively).[42] Any positive serum Galactomannan antigen in severe influenza mandates immediate antifungal treatment.[28] Recently introduced lateral flow device tests for detection of *Aspergillus* antigens in serum and BAL generate the results within 30 min.[43] Plaques in the trachea or bronchi noted during bronchoscopy in 15% may represent aspergillus tracheobronchitis. Bronchoscopy has been recommended by the Infectious Disease Society of America (IDSA) in suspected IPA.[44]

ANTIVIRAL AGENTS

Neuraminidase inhibitors (zanamivir, oseltamivir, peramivir, and laninamivir), adamantanes (amantadine and rimantadine),[45] and endonuclease inhibitors[46] (recently approved baloxavir) are the three classes of antiviral drugs available for the treatment and prevention of influenza. There is generally cross-resistance between oseltamivir and peramivir, attributed to the similarity in their chemical structure. Histidine to tyrosine substitution at amino acid 275 (H275Y) mutation is the most common mutation at the conserved active site of the neuraminidase. It confers high levels of resistance to both these drugs. Resistance to zanamivir has been minimal to date, with no major report of cross-resistance due to H275Y mutation. E119D/G mutations have been associated with resistance to multiple neuraminidase inhibitors in pandemic H1N1 isolates.[47] Single-point mutations (most common at position 31) in the codons for amino acids of M2 protein affect the transmembrane portion of this protein and confer cross-resistance to both amantadine and rimantadine.[48]

THERAPEUTIC CHALLENGES IN IMMUNOCOMPROMISED HOST

Patient-related issues are lack of typical clinical presentation, coinfection, poor response to vaccination, prolonged influenza shedding, and potential for spreading

resistant strains in the community. Pathogen-related issues are that the virus shows constant intrahost evolution, antigenic drift within the same ICH, development of antiviral resistance after therapy,[8,49] and simultaneous coinfection with two influenza subtypes.[50] The net outcome is diagnostic delay, treatment delay, and increased morbidity and mortality.

For severe ICH (like those receiving chemotherapy for malignancies, hematopoietic, or SOT recipients) who present with an acute respiratory illness, prompt antiviral therapy initiation has been recommended.[51] Benefit of such intervention is seen thus. SOT recipients pH1N1 influenza who received antiviral therapy within 48 h of symptom onset showed lower ICU admission compared with those receiving antiviral therapy later (8% vs. 22%).[12] In a retrospective study of HSCT recipients with influenza, early antiviral therapy for upper respiratory tract disease within 48 h of diagnosis predicted reduced risk of progressing to lower respiratory tract disease, hypoxemia, and overall death.[52] Among pregnant women with pH1N1 influenza, delay of antiviral therapy initiation >4 days after symptom onset was associated with increased admission to ICU than those who began therapy within 2 days (57% vs. 9%).[16] Similar delay in severely ill pregnant women with pH1N1 influenza increased the mortality in another study.[17] Overall, critically ill patients of any etiology benefited from early antiviral initiation for suspected or confirmed influenza.[33] Antiviral treatment may be required for >5 days.[53]

Limited data are avaailable on the response of influenza infection to combination antiviral therapies in ICH. Six patients in a pilot study received triple combination therapy with amantadine, oseltamivir, and ribavirin. Clinical response was favorable, and pharmacokinetics were safe. However, the sample size was too small to generalize these findings or make recommendations.[54] Barring this study, we found no major study supporting combination therapy in influenza.

Due to widespread resistance, adamantanes are no longer recommended[53] and warrant no further mention. Oseltamivir resistance due to H275Y mutation has already been discussed. In such cases, the possibility of cross-resistance to peramivir renders it ineffective.[55] Intravenous zanamivir was earlier approved for oseltamivir-resistant cases.[56] However, it is currently available only as inhaled preparation. Its use in patients with severe respiratory illness and chronic respiratory conditions such as asthma, obstructive airway disease is not recommended.[45] Intravenous peramivir was approved in 2014 by the US Food and Drug Administration (FDA) for treating uncomplicated influenza infection in adults who have been ill for ≤48 h.[57] Laninamivir was approved for use in Japan in 2010 and is in Phase III clinical trial of the WHO.[58] Baloxavir was approved in October 2018 by the FDA for the treatment of acute uncomplicated influenza in adults and children ≥12 years of age who have been symptomatic for ≤48 h.[46]

Several adjunctive approaches have been evaluated including extracorporeal membrane oxygenation (ECMO), N-acetyl cysteine, intravenous immunoglobulin G (IVIG), and glucocorticoids. Table 1 outlines treatment options in influenza A (H1N1). Recent reviews found no benefit from steroid use in severe influenza.[59,64] In ICH steroids, possibly increase co-infection by downregulating innate and adaptive immunity (like in IAA).[28] Sporadic reports show its beneficial use in organizing pneumonia,[65] postviral inflammatory pneumonitis,[66] and influenza A (H1N1) pneumonia in a pregnant woman.[67]

Conventional positive pressure ventilation leads to exacerbation of lung injury due to barotrauma, volutrauma, biotrauma, and toxicity from high oxygen concentrations. These issues can be mitigated by ECMO. However, the exact mechanism and usefulness of ECMO in severe ARDS in ICH are not clear. The conventional ventilation or ECMO for severe adult respiratory failure trial clearly demonstrated survival benefit at 6 months using ECMO.[68] Extracorporeal Life Support Organization (ELSO) registry report showed overall survival rates of up to 67% in 2009.[69] Subsequent benefit of ECMO was noted, especially in viral pneumonias.[68,70,71] However, ECMO in ICH was one of the poor prognostic factors.[72,73] As per the ELSO guidelines, presence of leukopenia (neutrophils <500 mm³) or other immunocompromising conditions may be a contraindication for ECMO, but this is not clearly defined.[69] Despite this, Pham *et al*. performed ECMO in an ICH group. Markedly lower mortality rates were seen in younger patients managed with ECMO despite severe respiratory failure.[74] In a review of ECMO for managing ARDS in ICH, an overall mortality rate of 61.1% was seen.[61] Interpretation and extrapolation of this result is debatable.

DRUG RESISTANCE IN IMMUNOCOMPROMISED HOST

Resistance mutations to oseltamivir and/or zanamivir emerge more commonly in ICH probably due to prolonged viral shedding despite antiviral therapy.[49,75,76] It poses a new threat of development and community spread of resistance. One study found all influenza viruses identified in ICH group to be resistant to at least one class of antiviral agents. Four percent of the viruses were resistant to neuraminidase inhibitors as well as adamantanes. ICH group that received a prolonged course of antiviral therapy (>5 days) showed greater tendency to harbor resistant viruses.[8]

PROGNOSTIC FACTORS FOR INFLUENZA A (H1N1) IN IMMUNOCOMPROMISED HOST

Factors independently associated with mortality in ICH with influenza A (H1N1) are male sex, high Acute Physiologic Assessment and Chronic Health Evaluation II score, use of corticosteroids, and vasopressor support.[2] Delayed antiviral therapy beyond 48 h of symptom onset

Table 1: Treatment options in influenza

Treatment	Comment	Role in ICH
Antivirals		
Oseltamivir	Unpredictable absorption in graft versus host disease of gut[53,60]	Yes, usually required to continue for >5 days
Zanamivir	Intravenous preparation was discontinued but is now again under study[45]	No evidence-based recommendation, but tried as part of combination regimen
Peramivir	Use in children and severe influenza is yet to be studied[57]	No specified role
Laninamivir	Phase III trial ongoing[58]	Not applicable
Baloxavir	US-FDA approved in 2018[46]	No specified role
Steroid	Not recommended[59]	No role; can increase coinfection by downregulating innate and adaptive immunity[28]
Extracorporeal membrane oxygenation	Investigational	No evidence-based recommendation. But mortality benefit seen in influenza-related ARDS including ICH[61]
IVIG	Investigational	High-dose IVIG can be tried in children with severe influenza, especially ICH[62]
N-acetyl cysteine	Anecdotal[63]	No evidence-based recommendation

ARDS: Acute respiratory distress syndrome, IDSA: Infectious diseases society of America, IVIG: Intravenous immunoglobulin G, US-FDA: United States Food and Drug Administration, ICH: Immunocompromised host

also correlates with poor prognosis.[52] Thus, the initiation of antiviral treatment at the earliest suspicion of influenza in ICH is advisable.

PREVENTION STRATEGIES USED IN IMMUNOCOMPROMISED HOST

An 8-year long study has demonstrated beyond doubt the positive effects of vaccination in health-care workers (HCWs) on reduction in nosocomial influenza in cancer patients. Policy changes have included signage throughout the institution to remind patients, family members and caregivers to cover their cough during the influenza season, and frequent hand hygiene and refrain from touching their mucous membranes (eyes, nose, and mouth) while in hospital. Screening of visitors for upper respiratory tract infection (URTI) and restrictions on visiting high-risk patients have proven effective. HCWs with URTI are encouraged to use mask. HCWs with fever >38°C and uncontrollable secretions, cough, or other communicable respiratory symptoms are excluded from direct patient care until 24 h after resolution of fever in the absence of antipyretics.[77] ICH with influenza A (H1N1) should ideally be housed in a room with positive airflow. Restricted access minimizes nosocomial spread of the virus.[29] At the community level, a combination of hand hygiene and face masks, implemented within 36 h of symptom onset in the index patient, has prevented household transmission of seasonal influenza.[78]

CHEMOPROPHYLAXIS IN IMMUNOCOMPROMISED HOST

For an ICH at high risk of complications from influenza or their unvaccinated close contacts, chemoprophylaxis is advisable if close contacts are diagnosed with influenza. Oseltamivir within 48 h of exposure and continued for 10 days is recommended. This recommendation is independent of the previous vaccination status of the ICH.[60]

VACCINATION IN IMMUNOCOMPROMISED HOST

Due to the constantly evolving influenza virus, restructured vaccines against prevalent strains have to be developed and deployed periodically. We restrict ourselves to reviewing the Centers for Disease Control and Prevention (CDC) guidelines for influenza vaccine for 2018–2019 in ICH[79] and IDSA guidelines of 2013 for vaccination in ICH.[80] The latter have remained unchanged and have been used by CDC for 2018–2019. CDC advises against the use of live attenuated influenza vaccine in ICH and their close contacts including family members and HCWs. ICH have higher risk for disease attributable to the vaccine virus and blunted immune response to such vaccines. CDC recommends annual use of inactivated influenza vaccine (IIV) or quadrivalent recombinant influenza vaccine (RIV4) in an ICH and their close contacts.[79]

The IDSA recommends annual vaccination with IIV in ICH aged ≥6 months. This group includes HIV-infected patients, those with solid organ malignancy, hematological malignancy, and patients on chronic immunosuppressive therapy. For HSCT recipients, IIV is recommended for persons aged ≥6 months starting 6 months after HSCT. In SOT recipients, IIV is best provided between 2 and 6 months after transplant. Exceptions to receiving IIV in ICH are patients who are very unlikely to respond (although unlikely to be harmed by IIV), such as those receiving intensive chemotherapy such as for induction or consolidation chemotherapy in acute leukemia or those who have received anti-B-cell antibodies within 6 months.[79]

FUTURE DIRECTIONS

Guidelines on the range of use of newer antivirals such as peramivir, laninamivir, and baloxavir are eagerly awaited. Efficacy of combination therapies in ICH will be soon clear. Prospective studies for the use of steroid in severe influenza, and especially ICH are urgently required given

the widespread misconceptions and variations in treatment policies regarding its use. Role of ECMO and other novel therapies such as IVIG and N-acetyl cysteine if proven effective might open uncharted territories.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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