Chapter 45
Emerging Respiratory Pandemics

Seema Oommen

Key Points
- Since the identity of the respiratory pathogen is not known at the time of admission, emergency department personnel and intensive care staff are at the highest risk of exposure while handling such patients.
- Physical signs in respiratory pandemics are minimal in contrast to the radiological signs.
- Rapid respiratory deterioration necessitating intensive care is a common feature early in the disease.
- Contact, droplet and airborne barrier precautions are necessary to prevent the spread of infection within the hospital.

Introduction

Over the last two decades, there has been an increase in the incidence of emerging and remerging respiratory viruses, primarily of zoonotic origin, capable of causing respiratory infections of pandemic proportions.

The leading pandemic of the new millennium was that of a novel coronavirus called severe acute respiratory syndrome coronavirus (SARS-CoV). It originated in the live game markets in the Guangdong province of southern China in the late 2002 and affected about 8,096 people in over 30 countries, of which 774 died till early 2004 [1]. Palm civets sold in these markets are considered as the source of this infection.

S. Oommen, MBBS, MD, DNB
Department of Microbiology, Pushpagiri Medical College Hospital,
Tiruvalla, Kerala 689101, India
e-mail: seema.oommen@gmail.com
Swine flu is the popular name of the relatively new strain of influenza A/2009/H1N1 that caused a pandemic which began in Mexico and spread rapidly from there across the world in 2009–2010. More than 600,000 laboratory-confirmed cases were reported from more than 200 countries worldwide as of March 2010 with a total of 18,449 deaths as reported by the World Health Organization (WHO) in August 2010 [2]. This is considered an under-representation of the actual numbers as many deaths were never tested or recognized as influenza related [2]. Meanwhile new cases of H1N1 are being diagnosed worldwide including India in 2014.

The WHO estimates a total of 676 laboratory-confirmed human cases of avian flu (H5N1) infection and 398 related deaths in 16 countries from 2003 to 2014 [3]. Avian influenza viruses are divided into the high pathogenicity H5N1 virus with 100% mortality in the poultry and low pathogenicity H7N9 viruses not associated with severe disease in poultry. Cases of H7N9 are reported mainly from the People’s Republic of China.

The most recent respiratory illness was first reported in Saudi Arabia in 2012 and is of a new strain of coronavirus called the Middle East respiratory syndrome coronavirus (MERS-CoV) that shares a genetic relatedness to a similar virus found in camels. By June 2014 there were around 699 laboratory-confirmed infections with 209 deaths [4]. The majority of these cases were from the Middle East countries with few cases in the USA, Europe, Malaysia and the Philippines in Asia.

Thus the crude case fatality rate of H5N1 is highest at 60%, followed by MERS-CoV (30%), SARS-CoV (10%) and the least H1N1 (0.5%), the latter being most likely under-represented [1–4].

Pathophysiology

Adaptation of the viruses by mutation or reassortment leading to an ability to cross the species barrier into humans, the capability to become established in humans and a sustained ability to pass from one human to the other are the three features needed to cause an infectious disease of epidemic proportions. Combine this with the increased mobility of individuals across the world; transfer of these infections from one part of the globe to the other can take place in a relatively short period of time.

Direct lysis of the host cells is one of the mechanisms of host tissue damage. More important are the indirect consequences of the host immune response which get disrupted, tipping the balance from being favourable to an exaggerated and destructive host immune response leading to an outpouring of pro-inflammatory chemokines and cytokines termed as ‘the cytokine storm’ [5].

Cytokines like tumour necrosis factor alpha (TNF α), interleukin 6 (IL-6), IL-1β and IL-8 play a major role in tissue damage [5]. Of this IL-1β has been found to be the main cytokine in the broncho-alveolar lavage (BAL) fluids of patient with lung injury [5].
The net result is local diffuse damage to the alveoli (acute lung injury – ALI) due to increased arrival of leucocytes, dilatation of blood vessels and tissue oedema and can swiftly progress to the more severe acute respiratory distress syndrome (ARDS). Spillover of these cytokines into the systemic circulation leads to multisystem organ failure and finally death.

Clinical Features

There is a considerable overlap in the clinical presentation by the common respiratory viruses and other atypical causes of community-acquired pneumonia making arousal of suspicion in the treating physician of an emerging epidemic virus unlikely. Hence suitable samples may not be collected at the appropriate time leading to misdiagnosis and a delay initiation of therapy.

- The common clinical presentation [1, 6, 7] of most respiratory pandemic viruses is that of an ‘influenza-like illness (ILI)’: an acute respiratory infection with sudden onset of fever (temperature of >38 °C or >100.4 °F), chills, myalgia and a non-productive cough. Sore throat and rhinorrhoea may also be present. Many cases are associated with gastrointestinal symptoms like abdominal pain and diarrhoea.
- A history of contact, in the preceding 10 days of symptom onset with poultry or with a known case in the countries detected to have human avian influenza cases, has to be elicited. Likewise, history of travel to the Middle East countries should arouse suspicion of a MERS-CoV infection.
- Cases may range from a mild ILI to a fulminant viral pneumonia. Rapid clinical deterioration may occur with diffuse viral pneumonitis with hypoxaemia, acute respiratory distress syndrome (ARDS), septic shock, multisystem organ failure and death occurring within a week of onset of illness [7].
- Secondary bacterial pneumonia especially due to Staphylococcus aureus, S. pyogenes and S. pneumoniae is a common complication with influenza [7].
- Extremes of age; pregnancy; obesity; presence of pulmonary, cardiac, hepatic, renal or metabolic co-morbidities; and underlying neurological conditions are the common risk factors for severe disease [1, 6].
- Case fatality of H5N1 is much higher than seasonal influenza viruses with rapid clinical deterioration mainly due to early involvement of the lower respiratory tract.

Investigations

Considering the rapid spread of virus in the past within hospitals and community, methods to rapidly identify infected cases are of utmost importance.
**Molecular Diagnostic Methods**

- The real-time-based polymerase chain reaction (RT-PCR)-based assay is one such means which has proven its worth both during the SARS-CoV and the H1N1 outbreak. The only caveat is that appropriate clinical samples need to be collected at the appropriate time during the disease and should be transported to the laboratory in cold chain in a viral transport medium so as to maintain the viability of the nucleic acid.

- Multiplex PCR can detect simultaneously other viruses causing a similar clinical picture like the seasonal influenza A and B, respiratory syncytial virus (RSV) and human metapneumovirus.

- The most preferred specimen is a nasopharyngeal aspirate or a swab preferably within 1–2 days of onset of disease [6]. Cotton swabs are not recommended due to presence of inhibitors; rayon- or nylon-flocked swabs are used instead. Broncho-alveolar lavage, tracheal aspirates and sputum which contains the highest viral loads are the ideal specimens especially later in the course of illness [6].

- RT-PCR tests may be carried out on serum specimens.

- In case of suspicion of MERS-CoV or SARS-CoV, stool specimens may also be sent to the laboratory.

- Many a times these newer molecular assays may not be available even in established diagnostic molecular laboratories and the specimen may have to be shipped under strict biohazard protocols to the national or a regional reference centre for testing.

---

**Other Diagnostic Tests**

- Rapid diagnostic tests available for the diagnosis of influenza have high specificity but low sensitivity and hence a negative result should be interpreted with care [7].

- Though viral cultures don’t play a significant role in rapidly diagnosing cases, it is important in confirmation of emerging and re-emerging cases of viral infection, epidemiological typing of isolates and research into vaccines and newer drugs.

- Clinical signs on examination are minimal when compared to the radiological findings of the chest. Chest X-rays typically show diffuse interstitial infiltrates, unilateral or more commonly bilateral ground-glass opacities to focal consolidation that is seen early in the disease [1, 6, 7]. These opacities are usually seen in the lower lungs first and may become widespread affecting larger areas as the disease progresses. High-resolution computed tomography may be required in ambiguous cases.
Tests done to rule out other infectious aetiology include blood cultures, Gram’s stain and culture of the sputum and urinary antigen detection for legionella and pneumococci. Acute and convalescent serum samples may be collected for antibody detection of various pathogens.

Healthcare personnel should be on high alert in the present global climate for any clustering of similar cases. Picking up a probable epidemic early in its course may limit the spread of the infection within the hospital and the community.

Treatment

Treatment is largely supportive for uncomplicated cases, also bed rest and maintenance of hydration, in addition to analgesics and antipyretics. Severe cases require supportive measures including ventilation and antibiotics for secondary bacterial infections.

Antivirals

- Oseltamivir and zanamivir [6, 8] are neuraminidase inhibitors that decrease the release of influenza viruses from infected cells, thus limiting its spread. It has been used extensively in the 2009 H1N1 pandemic. Resistance to oseltamivir has been documented [8]. Best results were obtained when treatment was started within 48 h of symptom onset even before the availability of laboratory results.
- The dosage of oseltamivir for persons above 13 years of age and >40 kg weight is 75 mg twice daily for duration of 5 days.
- For children <15 kg, the dose of oseltamivir is 30 mg twice a day, 15–23 kg is 45 mg twice a day and >23–40 kg is 60 mg twice daily.
- Zanamivir is advised for persons above 5 years of age at a dose of 10 mg (two inhalations) twice a day. Oseltamivir is the drug of choice to treat human cases of avian influenza.
- Unlike influenza there is no specific antiviral or vaccine available for the coronaviruses. A combination of ribavirin and interferon 1α shows synergistic action in vivo and has been used to treat MERS-CoV and SARS-CoV infections but limited data is available on their effectiveness to combat the disease and clinical trials are needed to demonstrate their effectiveness [1].
- Steroids were used during the SARS outbreak to limit the cytokine-mediated lung injury in conjunction with ribavirin but the actual role of steroids has to be elucidated with further studies. Steroids are contraindicated in cases of influenza pneumonia as it may further predispose to secondary bacterial infection.
Prevention

- The incubation period for most influenza viruses including H1N1 is 1–4 days [7], whereas the incubation period for H5N1 is slightly longer ranging from 2 to 8 days.
- Patients with influenza are most infectious in the first 2 days of the onset of illness averaging from a day before the onset of symptoms to 5–7 days after the onset of illness.
- The incubation period of coronaviruses like SARS-CoV and MERS-CoV is around 2–14 days. In contrast to influenza cases, they transmit the virus usually after the fifth day of the onset of disease when viral load maximizes in the nasopharyngeal secretions [1].

Prophylaxis

1. Immunoprophylaxis [9]: Exists currently only for influenza. It is advised by the Advisory Committee on Immunization Practices (ACIP) that all persons over 6 months of age be vaccinated annually against the predicted influenza strains which are most likely to cause infections in the next influenza season based on surveillance data. It is available as an annual influenza vaccine incorporating three or four live attenuated or inactivated influenza strains. It is available for administration as nasal sprays (live attenuated vaccine) and the intramuscular or intradermal route (killed vaccine).

2. Chemoprophylaxis [7]:
   - Oseltamivir and Zanamivir (neuraminidase inhibitors) are active against both influenza A and B viruses. It is indicated in exposed unvaccinated immunocompromised persons or people with co-morbid conditions who are at a high risk of developing influenza.
   - Oseltamivir should be given within 1 day after exposure at a dose of 75 mg once daily for persons 13 years and above of age for a minimum of 10 days after exposure to a recent contact with a known case of influenza.
• Zanamivir is prescribed at two inhalations once daily for people above 5 years of age. If the exposed person develops respiratory symptoms, he should be given treatment doses of the drug.
• In case of H5N1, close contacts of strongly suspected cases of human avian influenza and personnel handling infected poultry are advised oseltamivir as chemoprophylaxis [10].

3. Standard contact, droplet and airborne precautions [11]:

Oftentimes, emergence of an infection of pandemic potential is not routinely expected by physicians and staff in their regular days’ work. But going by the past experience especially in case of SARS-CoV, healthcare personnel were the ones at high risk of infection given the close proximity to the patient. Hence it is important that all staff follow the standard contact and droplet precautions for any case suspected to have a respiratory infection.

• Contact and droplet precautions include wearing of personnel protective equipment (PPE) such as gloves, gowns, eye and face shields.
• There is special emphasis on hand hygiene which must be diligently performed before and after contact with the patient, the potentially infectious material generated by him, before wearing and after removing PPE.
• Airborne precautions include placement of patients in an airborne infection isolation room (AIIR) and wearing of N95 or greater respirators and masks. Airborne transmission is especially possible while suctioning a ventilated patient, bronchoscopy, sputum induction, intubation and extubation and cardiopulmonary resuscitation.
• Pending placement of patient in the AIIR a face mask must be placed on the patient and the patient isolated in a single room to prevent spread of infection.
• Environment infection control must be followed per hospital infection control policy using a suitable disinfectant for disinfection and collection, transport and treatment of all infectious waste generated.
Summary and Algorithm

Patient presenting with 'influenza like illness' and chest radiograph showing signs of pneumonia necessitating hospitalization

Elicit travel history to Middle Eastern countries for MERS-CoV and or history of contact with poultry for H5N1. Physicians and staff to be alert on clustering of similar cases in the recent past

Inform district health authorities.

Always maintain personnel protection: contact, droplet and airborne precautions to be practised.

Isolate the patient. Place a mask on the patient pending isolation

Collect appropriate specimens to confirm diagnosis and to rule out alternate diagnosis.

1. Nasopharyngeal aspirates, swabs, BAL for molecular testing of influenza, RSV, human metapneumoviruses, MERS-CoV and H5N1 as deemed appropriate
2. Blood cultures
3. Sputum gram stain and culture
4. Urine antigen detection
5. Serum for antibody/antigen detection
6. Other routine tests like complete blood count etc

If clinical suspicion of Influenza is high initiate treatment with Oseltamavir

Laboratory results like molecular tests and blood cultures are usually available after 72 hours
References

1. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev. 2007;20(4):660–94.
2. Pandemic (H1N1) 2009 - Update 112. http://www.who.int/csr/don/2010_08_06/en/. Last accessed 05 Jan 2016.
3. Influenza at the human-animal interface. Summary and assessment as of 4 December 2014. Human infection with avian influenza A (H5N1) viruses. http://www.who.int/influenza/human_animal_interface/Influenza_Summary_IRA_HA_interface_04December2014.pdf?ua=1. Accessed 05 Jan 2016.
4. Middle East respiratory syndrome coronavirus (MERS-CoV) summary and literature update–as of 11 June 2014. http://www.who.int/csr/disease/coronavirus_infections/MERS-CoV_summary_update_20140611.pdf. Last accessed 10 Jan 2015
5. Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biol Rev. 2012;76(1):16–32.
6. Cheng VC, To KK, Tse H, Hung IF, Yuen KY. Two years after pandemic influenza A/2009/H1N1: what have we learned? Clin Microbiol Rev. 2012;25(2):223–63.
7. Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Bautista E, Chotpitayasunondh T, Gao Z, Harper SA, Shaw M, Uyeki TM, Zaki SR, Hayden FG, Hui DS, Kettner JD, Kumar A, Lim M, Shindo N, Penn C, Nicholson KG. Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection. N Engl J Med. 2010;362(18):1708–19.
8. Fiore AE, Fry A, Shay D, Gubareva L, Breshe JS, Uyeki TM, Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza. Recommendations from the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60(1):1–24.
9. Centers for Disease Control and Prevention (CDC). Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices – United States, 2013–2014. MMWR Recomm Rep. 2013;62(RR-07):1–43. Erratum in: MMWR Recomm Rep. 2013;62(45):906.
10. WHO rapid advice guidelines on pharmacological management of humans infected with avian influenza A(H5N1) virus. Available at http://whqlibdoc.who.int/hq/2006/WHO_PSM_PAR_2006.6_eng.pdf?ua=1. Last accessed 10 Jan 2015.
11. CDC and Healthcare Infection Control Practices Advisory Committee (HICPAC). 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf. Last accessed 05 Jan 2016.